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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(54) Title: METHOD AND APPARATUS FOR MEASURING LOCALLY AND SUPERFICIALLY THE SCATTERING AND ABSORPTION PROPERTIES OF TURBID MEDIA

(57) Abstract

We present a method and apparatus for local and superficial measurement of the optical properties of turbid media. The depth probed is on the order of 1 transport mean free path of the photon. The absorption coefficient, reduced scattering coefficient and the phase function parameter $\gamma = (1-g_2)/(1-g_1)$ are optical parameters computed from a single measurement of the spatially resolved reflectance close to the source. Images of superficial structures of the medium can be obtained by performing multi–site measurements. An important application of this technique is the characterization of biological tissues, for example for medical diagnostic purposes. Measurements on biological tissues can be achieved using a probe of diameter less than 2mm, and the average volume probed is on the order of 1 mm^3. Separate images of absorption and tissue structure can be achieved with a resolution of approximately one transport mean free path of the considered tissue.

R(ρ) depends on μ_s, μ_a and p(θ)

METHOD AND APPARATUS FOR MEASURING LOCALLY AND SUPERFI-
CIALLY THE SCATTERING AND ABSORPTION PROPERTIES OF TURBID
MEDIA

5   1. Field of the invention

The present invention relates to a method and an apparatus to quantify the optical scatter-

ing and absorption properties of a turbid media. More precisely the present invention

relates to a non-invasive measurement, over a small area of the sample surface. Local and

superficial characterization of biological tissues in vivo is a major application of this

10   invention.

2. Related Background Art.

Different techniques have already been proposed to quantitatively determine the absorp-

tion and reduced scattering coefficients of turbid media[1]. Most of the non-invasive meth-

ods are based on the measurement of spatially and/or temporally-resolved reflectance. The

15   principle is as follows: the turbid medium is illuminated by a light source. The backscat-

tered light is measured by one or several detectors. Different types of measurements are

possible, depending on the time-dependence of the illuminating source: steady-state (con-

tinuous source), time-domain (short pulsed source) or frequency domain (amplitude mod-

ulated source). The present invention relates to the case of steady-state measurements,

20   performed at different distance ρ between the source and the detectors. However, the tech-

nique presented here can be complemented by time- or frequency-domain measurements.

The range of ρ values is an important point to consider, when comparing different meth-

ods based on the measurement of the reflectance. First, the probed volume of the turbid

medium is related to the source-detector separation ρ. The larger the source-detector separation, the deeper the average depth probed. Second, depending on the range of ρ, different mathematical processing must be used to obtain the optical properties from the raw data. At least two cases must be distinguished.

5   1) The first case corresponds to source-detector separations larger than several transport mean free paths. For typical biological tissue optical properties[2], this case correspond to source-detector separation of larger than 2 mm. An analytical form of the reflectance can be obtained from the diffusion equation, if the absorption coefficient μ_a is sufficiently lower than the scattering coefficient μ_s (typically at least ten times). In such a case, the rel-

10   evant optical properties are the refractive index, the absorption coefficient and the reduced scattering coefficient. The average depth of probing is on the same orde ρ than the source-detector separation.

Such methods have been already published, and are the object of patents (Ref.1, Patent 5,517,987 Tsuchiya, Patent 5,676,142 Miwa et al.).

15   2) The second case corresponds to source-detector separations close to one transport mean free path. For biological tissues[2], such source-detector separations correspond typically to distances from 0.1 to 2 mm. The average depth probed is on the order of 1 mm. Such small source-detector separations enable the measurement of the optical properties of a small tissue volume.

20   In this case, light propagation can be modeled using Monte Carlo simulations. In contrast to the previous case 1), it was discovered by the inventors that not only the first moment of the phase function must be considered, but also the second moment. More precisely, the relevant optical properties are the refractive index, the absorption, the reduced scattering

coefficient and the parameter $\gamma=(1-g_2)/(1-g_1)$, that takes into account the first two moments of the phase function, denoted g_1 and g_2 respectively.

Different methods have been proposed for local characterization of turbid media, and in particular of biological tissues. Nevertheless none allows for the simultaneous determina-

5   tion of the absorption, the reduced scattering coefficient and the parameter γ. Wang et al. (Patent 5,630,423) proposed a method for the determination of the reduced scattering coefficient only, using an optical beam of oblique incidence. Moreover, their analysis does not include the effect of the phase function. Kessler et al. (Patents 5,284,137 and 5,645,0619) proposed a method for measuring the local dye concentration and scattering

10   parameters in animal and human tissues, based on spatial and spectral measurements. However, their methods do not enable the simultaneous determination of the absorption coefficient, reduced scattering coefficient and the parameter γ.

In the present invention we present a method and apparatus for the measurement of the absorption coefficient, the reduced scattering coefficient and the said phase function

15   parameter γ, from the spatially-resolved reflectance data at short source detector separation. These three parameters, which can be measured at different wavelengths, enable us to characterize turbid media, such as biological tissues. Our method is based on a theoretical study of the reflectance at short source-detector separations, that we performed with Monte Carlo simulations. Other publications may be of concern:

20   1. See "Welch, A. J.; van Gemert, M. J. C. Optical Thermal Response of Laser Irradiated Tissue; Plenum publishing Corp., New York, 1995", and references therein.

2. W.-F. Cheong, S.A. Prahl, and A.J. Welch, "A Review of the Optical Properties of Biological Tissues," IEEE J. Quantum Electron. 26, 2166-2185 (1990).

BRIEF DESCRIPTION OF THE DRAWINGS

Fig.1.Description of the principle of spatially-resolved reflectance measurement.

Fig.2. Probability density function of the mean depth of scattering events per detected photons.

Fig.3. Examples of reflectance obtained with different phase functions. Case of matched refractive index (n=1.0).

Fig.4.Monte Carlo simulations and fits on the form $R(\rho) \cong [A(\rho, \mu_s', \gamma) + \mu_s' B(\mu_a)]^2$. Case of constant $\gamma=1.9$ and $\mu_s'=1$ mm^{-1}, numerical aperture of the source and detectors = 0.37. A = $0.0647\rho^{0.324}\exp(-0.161\rho)$, B = $0.18653 \mu_a - 0.8466 \mu_a^2 + 1.836\mu_a^3$

Fig.5.a. Basic description of the apparatus: Case of measurement with an optical fiber probe

Fig. 5.b. Basic description of the apparatus: Particular embodyment where the probe is composed of n detecting fibers (typically 6). A broadband or white light source is used for excitation and the retrodiffused light is collected by the n detecting fibers and dispersed in parallel in a spectrograph, before being detected on a 2D CCD camera and transmitted numerically to a PC for γ, μ_s', μ_a determination at each wavength λ .

Fig. 5.c. Basic description of the apparatus. Case of measurement with sources and detectors directly in contact with the turbid medium.

Fig. 5.d. Basic description of the apparatus. Case of non-contact measurements with a 1D or 2D detector, coupled with an imaging device. Scanning systems 1 and 2 are optional, they may be distinct from one another or confounded in a single scanner.

Fig. 5.e Basic description of the apparatus. Case of non-contact measurements with source and detection beams deflected by one or two scanning devices which may be distinct from one another or confounded.

Fig.6.Examples of the sample side of the fiber optical probe.

6a. simple arrangement for a single measurement.

6b. arrangement for symmetrical measurements.

6c. Arrangement for multiple measurements.

6d. Arrangement for multiple measurement, using an multicore fiber, or an optical fiber bundle.

6e. Arrangement for symmetrical measurements where detecting fibers are arranged on an elliptic path so as giving a regular spacing from the illuminating fibers to the detecting fibers, while maximizing the collecting surface of the fibers. Additional fibers F can be put in the center of the probe or around the probe for other light channels: collecting fibers for fluorescence or Raman scattering for example.

Fig.7.Example of an measured the spatially-resolved reflectance with the probe shown in Fig.6a. The measurement, performed on a microsphere suspension, is superimposed to a Monte Carlo simulation. The optical properties, computed from published water optical properties (μ_a) and Mie theory (μ_s', γ) are: n=1.33, μ_a=0.0004 mm^{-1}, μ_s'=1.0 mm^{-1}, γ=2.2. The calibration was performed with a siloxane sample of known optical properties.

Fig.8.Relation between the parameters R(ρ=1 mm) and $|\partial\rho\ln R(\rho=1 \text{ mm})|$ and the optical coefficients μ_s' and μ_a. Case of γ =1.5 and 1.9. Probe of refractive index = 1.5, sample of refractive index = 1.4, optical fibers diameter = 200 µm, NA=0.37 (source and collection).

Fig.9.Plot of the parameter $\frac{\partial}{\partial\rho}\sqrt{R}$ for different γ values (1.0, 1.8, 2.5), different reduced albedo a' (1, 0.95, 0.9) and for fixedρ=1 mm. Mismatched refractive index n=1.4.

Fig.10Plot of $\sqrt{R(a'=1)}-\sqrt{R(a)}$ for different γ values and reduced albedo a', and for fixed ρ=1 mm. Mismatched refractive index n=1.4.

DETAILED DESCRIPTION OF THE INVENTION

1. Definitions

The concept of spatially resolved reflectance is illustrated in Fig.1. Consider light imping-

ing on a turbid medium (through air or through a light guide), in a given solid angle

ω_{source}. The spatially resolved reflectance $R(\rho)$ is defined by the backscattered light power

5   in a given solid angle $\omega_{detector}$, at a distance ρ from the source, per unit area and normal-

ized by the source power. The distance ρ is referred as the source-detector separation (also

in the case when light guides or imaging devices are used for the illumination and for the

collection of the backscattered light).

$R(\rho)$ depends on the optical properties of the turbid medium, defined below. Note that

10       $R(\rho)$ depends also on the source and detectors characteristics, i.e numerical aperture and

sizes.

It is commonly admitted that the fundamental optical properties of a turbid medium is

determined by the average index of refraction n of the medium, the absorption coefficient

μ_a, the scattering coefficient μ_s, and the phase function $p(\theta)$ where θ is the scattering

15   angle. The absorption coefficient μ_a [mm^{-1}] is defined as the probability of absorption per

unit infinitesimal pathlength. The scattering coefficient μ_s [mm^{-1}] is the scattering proba-

bility per unit infinitesimal pathlength. The phase function $p(\theta)$ is the density probability

function for the scattering angle θ. The phase function is normalized as follows:

20
$$1 = 2\pi\int_0^\pi p(\theta)\sin\theta\, d\theta . \tag{1}$$

The nth order moment g_n of the phase function is defined as:

$$g_n = 2\pi\int_0^\pi P_n(\theta)p(\theta)\sin\theta\, d\theta \tag{2}$$

where $P_n(\theta)$ is the Legendre polynomial of order n. The first moment of the phase function is also called the anisotropy factor, and is often simply noted g ($=g_1$). It represents the mean cosine of the scattering angle. The reduced scattering coefficient μ_s' is defined as:

$$\mu_s' = \mu_s(1-g_1) \tag{3}$$

5   The transport mean free path (or reduced mean free path) mfp' is defined as:

$$mfp' = (\mu_s' + \mu_a)^{-1} \tag{4}$$

The reduced albedo a' is the ratio:

$$a' = \mu_s'/(\mu_s' + \mu_a) \tag{5}$$

10   As a result of the present invention described in more details in the next section, it is also necessary to define another phase function parameter called γ:

$$\gamma = (1-g_2)/(1-g_1) \tag{6}$$

All the parameters listed above are referred as optical properties. They are wavelength dependent, and can vary in space and time.

15

2. Reflectance measurements at distances close to one transport mean free path

The methods described in the Patent 5,517,987 (Tsuchiya) are based on measurements with large range of source-detector separations, typically from 1 mfp' to 10 mfp'. In such cases, the volume probed is on the order of 10-1000 (mfp')^3. In contrast with such a large

20   scale investigation, the present invention is directed to a novel approach where the volume probed is much smaller, on the order of 1 (mfp')^3. This is achieved by using only small source detector separations, typically from 0.1 to 2 mfp'. The lateral dimension of probing is limited to this range of distances.

Note that the present invention can be complemented by large source-detector separation measurements, if the optical properties of both superficial and deep parts of a turbid medium must be determined.

A model of photon migration in tissue was necessary to predict the relationship between the measured reflectance and the optical properties. Analytical solutions from the diffusion equation are not appropriate in our case because we are interested in the reflectance close to the source, at distances comparable to the transport mean free path [mfp']. We have performed Monte Carlo simulations to predict the measured reflectance of an homogeneous semi-infinite turbid media.

The exact diameter of the illuminating and collecting fibers, as well as their numerical apertures, have been taken into account in the simulations. The mismatch of index of refraction at the surface of the medium have been also taken into account in the simulations, by using the Fresnel law for each photon reaching the surface.

This is also one result of this simulation to compute the average depth of probing, illustrated in Fig.2. It is demonstrated that only the superficial part of the turbid medium is probed if small source-detector separations are used. For this, we determined the depth below the surface of each scattering event in the simulation. With this information we determined the average depth of all the scattering events for each detected photon, which we present as a probability density function in Fig.2. This figure shows that the average depth of scattering is approximately around 1 mfp'. Moreover it showed that the part located below 2 mfp' were not playing a significant role in the measured signal (for $\rho < 1.5$ mfp').

The spatially resolved reflectance $R(\rho)$, with short source-detector separations is more

complex than in the case of large source-detector separations. Indeed, for small source detector-separation conditions, the inverse problem. i.e. calculating the localized absorption and reduced scattering coefficients. is sensitive to the scattering phase function. It is part of the present invention to have shown, from Monte Carlo simulations, that only the

5   first and second moments of the phase function can be taken into account. Moreover, it was established that the influence of the these two moments are not independent. Indeed, it is a merit of this invention to demonstrate that only one parameter $\gamma=(1-g_2)/(1-g_1)$, which depends on the first and second moments of the phase function can be used to characterize accurately the reflectance at short source-detector separation.

10   Fig.3 illustrates the fact that the parameter γ is the only predominant parameter of the phase function that must be taken into account (and not g_1 as frequently mentioned in literature). Different reflectance curves, obtained from Monte Carlo simulations are shown in Fig.3. Four different phase functions were used for the simulations. Three phase functions are characterized by $\gamma=1.25$, but different g_1 and g_2 values. Fig.3 shows that almost

15   identical reflectance curve are obtained for distances $\rho\mu_s'>0.3$, if the g_1 and g_2 are varied in such a way that the parameter γ stays constant ($\gamma=1.25$). For comparison, the reflectance computed with a different g value is also presented ($\gamma=2.25$). It appears then clearly that the parameter g plays a significant role in the reflectance.

The parameter γ depends on the characteristics of the set of scatterers inside the turbid

20   medium: shape, distribution of sizes and refractive index.

The possibility of determining this parameter γ is an important part of this invention, and has never been reported earlier. The determination of γ can be related to the microscopic structure of the sample, since γ is related to the sizes and refractive indexes of the scatters.

In most cases, the average refractive indices n and the source and detectors characteristics are fixed and known. In such case, only three parameters are determined from measurements at short source-detector separation: μ_a, μ_s' and γ.

It is important to note that the parameter γ, cannot be estimated if large source detector separations are used. Indeed, the reflectance is only sensitive to γ at short source-detector separation.

It was also derived from Monte Carlo simulations that the reflectance $R(\rho)$, for $\rho \approx 1 mfp'$, can be reasonably well approximated by the expression:

$$R(\rho) \cong [A(\rho, \mu_s', \gamma) + B(\mu_a, \mu_s')]^2 \qquad (7)$$

In many cases, we found that Equ.(7) can also be written as:

$$R(\rho) \cong [A(\rho, \mu_s', \gamma) + \mu_s' B(\mu_a)]^2 \qquad (8)$$

it is important for the description of the invention to evidence the fact that the function A depends on ρ, the scattering properties (i.e. μ_s' and γ) but not on μ_a. In contrast, the function B depends on μ_a and μ_s' but neither on γ nor ρ. An example of Equ.(8) is shown in Fig.4.

This formulation is of great help to solve the inverse problem, as described in section 5.3.

3. Apparatus

In the first embodiment, The apparatus can be divided in three parts, described in Fig.5.a. The first part is the illuminating system. Any light source can be used. For examples: a) white sources, such as halogen or xenon lights, metal halides or fluorescent or phosphorescent sources. b) sources such as lasers, laser diodes, optical fiber lasers, light emitting

diodes or superluminescent diodes. c) the sources described in point a) and b) where monochromators, filters or interference filters are added to select a given set of wavelengths.

In the first preferred embodiment, The light power is conducted to the investigated sample
5   by the probe, which is the second part of the apparatus. The probe is preferably made of optical fibers, to illuminate and to collect the backscattered light. But GRIN rods or other type of light pipes can also be used. Different possible arrangements of optical fibers are illustrated in Fig.6. Two different modes of measurements can be chosen. First, one fiber is used to illuminate the sample and at least two other fibers are used to collect the backscat-
10   tered light at two different distances. Second, one fiber is used to collect the light and at least two other fibers, located at two different distances from the first one, are used to illuminate sequentially the sample.

The arrangement of the different fibers can be replaced by any imaging system or image guide, such as multicore optical fibers, or optical fiber bundle.

15   The light collected by the probe is analyzed by the detection unit, which is the third part of the apparatus. If wide spectral light sources are used (such as halogen or xenon lights), a spectrograph can be put between the probe and the detector to get wavelength dependence of the backscattered signal (either in the source or detection unit). Any types of detectors can be used. For example, photodiodes, avalanche photodiodes or photomultipliers can be
20   assigned to each collecting fibers. Simultaneous detection of each collecting fiber can also be achieved using linear or two-dimensional detectors such as Charge-Coupled Detectors (1D or 2D), intensified CCD or array of photodiodes.

Aparticular embodiment is described in Fig. 5.b. : the probe is composed of n detecting

fibers (typically 6). A broadband or white light source is used for excitation and the retrod-
iffused light is collected by the n detecting fibers and dispersed in parallel in a spec-
trograph, before being detected by a 2D CCD camera and transmitted numerically to a PC
for γ, μ_s', μ_a determination at each wavelength λ. This particular embodiment has the

5   advantage of yielding the wavelength dependance of γ, μ_s', μ_a from a single measurement.
A second type of embodiment is presented on Fig. 5.c. The difference with embodiments
presented in Fig. 5.a. and Fig. 5.b. is that optionally no optical fibers, light pipes or grin
rods is used. The light source unit is directly in contact with the turbid medium, as well as
the detector unit. Collimating optics, microoptics or imaging optics (DOE for example)

10   can be put between the turbid medium and the actual light sources and detectors. The dif-
ferent type of sources and detectors cited in example for the first embodiment can be used
for the second type of embodiments. Hybrid design, such as arrangements involving both
direct contacts sensors or detectors and fibers, light pipes or grin rods are also included in
the present embodiment.

15   The third embodiment is described in Fig. 5.d.and Fig. 5.e. The only difference with the
first and second embodiment is that no contact measurements are performed. A collimat-
ing system allow for a point-like illumination on the turbid medium. An imaging system
enables the measurement of the spatial distribution of the reflectance. The detectors can be
either an array (1D or 2D) of detectors (Fig. 5.d) with optional scanning 1 and 2 which can

20   operate separately or can be confounded in a single scanner, or a single detector (Fig. 5.e).
In this last case, an scanning device is used to obtain the spatially-resolved reflectance. A
fiber bundle, multicore fiber or relay optics (grin rod or multiple lenses) can be put
between the focal point of the imaging system and the detector(s). The different type of

sources and detectors cited in example for the first embodiment can be used for the third embodiment.

Spatial images of the parameters μ_a, μ_s' and γ can be obtained by a series of measurements at different locations, that we call multi-site measurements. Some mechanical or optical scanning device can be used for this purpose. The resolution of such images is on the order of the mean source-detector separation used for a single site measurement. All three embodiments can be expanded to perform multi-site measurements, by duplicating and/or multiplexing the illuminating or measuring devices. For example, the optical fiber probes shown in Fig.6, can be duplicated and put side by side. The scanning system described in the third embodiment can also be expanded to perform multi-site measurements.

4. Normalization and calibration

The differences of transmission between each fiber are corrected by performing a measurement on a turbid phantom illuminated uniformly.

The background light, measured with the light source turned off, must be subtracted from the signal.

In order to perform absolute intensity measurements, a calibration is performed on a turbid medium of known optical properties. Examples of such a medium are: 1) solid or liquid turbid medium which properties have been measured by other techniques, or reported in the literature 2) water suspension of microsphere of known size distribution and refractive index. Absorbing dye may be added to the suspension. In case 2) the scattering properties are calculated from Mie theory, and the absorption coefficient is assumed to be equal to the water absorption coefficient, if no absorbing dye is added. If an absorbing dye is used,

the absorption coefficient can be measured by a spectrophotometer, before mixing the solution with any scattering materials.

A Monte Carlo simulation is performed with the optical properties of the calibration sample. The simulation is then divided by the experimental reflectance performed on the cali-

5 bration sample. The result, that must be independent of the source-detector separation, is defined as the calibration factor. Each new measurement is multiplied by the calibration factor.

An example of a measurement, after calibration, is shown in Fig.7. The measurement was performed with the apparatus described in the first embodiment, with a probe similar to

10 the one described in Fig.6.a. A prior calibration was performed on a solid turbid medium, which optical properties were measured by another technique (frequency domain measurement, cf. Ref1). The sample was a water suspension of polystyrene microsphere of 1 μm diameter. The measurement is compared to a Monte Carlo simulation performed with the scattering properties calculated from Mie theory and absorption coefficient of water.

15 Fig.7 shows an excellent agreement between the measurement and the simulation, which confirm the validity of our simulation model, experimental measurement and calibration.

5. Signal processing

5.1.Control of the homogeneity of the area probed

20 Artifacts during a measurement, for example due to bad contact between the probe and the sample, or heterogeneity of the sample, can be detected by the following optional procedure. Two illuminating fibers are disposed symmetrically in regard to the collecting fibers (see Fig.6b). If the sample is homogeneous, the reflectance curve should be identical with

either illuminating fiber. Therefore, heterogeneity of the investigated region or obstructions beneath the fibers are detected by comparing the two curves. If the two curves are sufficiently close, the measurement is validated and the average of the two curves is calculated.

5   5.2. Smoothing procedure and computation of the derivative of the curve.

Functions in the form $m_1\rho^{m_2}\exp(m_3\rho)$ were always found to fit well Monte carlo simulations for a restricted range of distances. Therefore, a smoothing of the experimental reflectance $R(\rho)$ can be processed by fitting $R(\rho)$ to $m_1\rho^{m_2}\exp(m_3\rho)$.

The determination of the slope of the logarithm $\frac{\partial}{\partial\rho}(\ln R(\rho,\mu_s',a',\gamma))$ is also derived from this

10   fit, using the following formula:

$$\frac{\partial}{\partial\rho}(\ln R(\rho,\mu_s',a',\gamma)) = \frac{m_1}{\rho} + m_2. \tag{9}$$

The slope of the square root of $R(\rho)$ can also be derived (the use of these slopes are described below in section 5.3):

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$$\frac{\partial}{\partial\rho}\sqrt{R(\rho,\mu_s',\mu_a,\gamma)} = \left(\frac{m_1}{\rho} + m_2\right)\left(\sqrt{m_1}\rho^{\frac{m_2}{2}}\exp\left(\frac{m_3\rho}{2}\right)\right) \tag{10}$$

5.3. Inverse problem

We developed different methods to solve the inverse problem, which consists in extracting optical coefficients from the reflectance data.

20   Method 1.

Monte Carlo simulations show that the measurements of the reflectance intensity $R(\rho)$ and the slope of $\ln R(\rho)$ (denoted $\partial\rho\ln R$), determined at a fixed distance ρ, can be used to derive μ_s' and μ_a for a given γ value. Fig.8 shows graphically the relationship between μ_s'

and μ_a and the two parameters $R(\rho=1 \text{ mm})$ and $|\partial\rho\ln R(\rho=1 \text{ mm})|$ in the case of for $\rho=1 \text{ mm}, \gamma = 1.5$ and 1.9. Note that any other choice of ρ is possible, as long as ρ is on the order of 1 mfp'. We see in Fig.8 that μ_s' and μ_a can not be determined uniquely if γ is unknown. Further insight for optimizing the inversion strategy is provided by three addi-

5   tional features of Fig.8.

First, the determination of μ_s' is only weakly influenced by γ. Indeed in Fig.8 the errors induced by error in γ are typically 10% for μ_s' around 1 mm^{-1}. Second, although absolute determination of μ_a is not possible when γ is not precisely known, relative absorption changes can be still evaluated. Third, the indetermination of the parameter γ may be

10   resolved by the values of $R(\rho)$ and/or $|\partial\rho\ln R(\rho)|$ at other distances. Therefore the following procedure can be used:

(1) determination of μ_s' and μ_a from $R(\rho=1 \text{ mm})$ and $|\partial\rho\ln R(\rho=1 \text{ mm})|$ for a set of values γ. For example: $\gamma=1.0, 1.1, 1.2,...,2.5$.

(2) simulations with the different sets of μ_s' and μ_a obtained from point 1)

15   (3) comparison between the simulations and the reflectance profile for distances $0.3<\rho<2$ mm.

This last step allows us to determine the correct values of γ, μ_s' and μ_a. Points 1 to 3 can be done iteratively to evaluate γ more precisely, using a finer discrimination of γ values.

This method described by the iteration of points 1) to 3) corresponds to finding a simula-

20   tion that fit closely a measured curve $R(\rho)$. This can also be achieved by directly compar-ing the measured curve $R(\rho)$, with a set of simulations, and finding the simulation that minimize the square of the differences between the measured and simulated curves.

Note also that the use of the reflectance intensity $R(\rho)$ and the slope of $\ln R(\rho)$ is equivalent

16

to the use of two intensities $R(\rho_1)$ and $R(\rho_2)$, measured at two close distances ρ_1 and ρ_2, respectively.

Method 2.

The inverse problem can also be performed, considering properties of $R(\rho)$ expressed by Equ.(7).

Indeed, it can be derived from Equ.(7) that the quantity $\frac{\partial}{\partial\rho}\sqrt{R(\rho,\mu_s',\mu_a,\gamma)}$ does not depend on the absorption coefficient μ_a:

$$\frac{\partial}{\partial\rho}\sqrt{R(\rho,\mu_s',\mu_a,\gamma)}= 2\frac{\partial A}{\partial\rho}(\rho,\mu_s',\gamma) \tag{11}$$

This property is confirmed in Fig.9, where the quantity $\frac{\partial}{\partial\rho}\sqrt{R(\rho,\mu_s',\gamma)}$, evaluated at $\rho=1$ mm, is plotted as a function of μ_s' for $\gamma=1$, 1.9 and 2.5 and reduced albedo a'=1, 0.95 and 0.9 (note that any other choice of ρ is possible, as long as ρ is of the order of 1 mfp').

In Fig.9, the parameter $\frac{\partial}{\partial\rho}\sqrt{R(\rho,\mu_s',\gamma)}$ clearly depends on μ_s' and γ. In contrast, the dependence on a' is almost negligible.

Therefore, γ and μ_s' can be derived from the parameter $\frac{\partial}{\partial\rho}\sqrt{R(\rho)}$, calculated from the experimental reflectance $R(\rho)$ (see section 5.2). Simultaneous determination of γ and μ_s' require values of $\frac{\partial}{\partial\rho}\sqrt{R(\rho)}$ at different distances ρ (at least two). If one of the parameters γ or μ_s' is already known, the determination of the other one can be obtained from the value of $\frac{\partial}{\partial\rho}\sqrt{R(\rho)}$ at a single distance.

Convenient analytical approximation of $\frac{\partial}{\partial\rho}\sqrt{R(\rho)}$ can be obtained by fitting Monte Carlo results to polynomial functions. For example, in the case of fixed $\gamma=1.9$, we obtained:

$$\mu_s'=0.9162-52.89x+1795x^2-18155x^3+65428x^4 \tag{12}$$

where $x = \frac{1}{2}\frac{\partial}{\partial \rho}(\sqrt{R(\rho)})$ at $\rho = 1$ mm. x is expressed in $[mm^{-2}]$ and μ_s' is expressed in $[mm^{-1}]$.

This results is valid for a probe of refractive index of 1.5 and a sample of refractive index of 1.4, optical fibers of diameter 200 μm, NA=0.37 (source and collection).

Once μ_s' and γ are calculated from the procedure explained above, μ_a is calculated from the absolute value of $R(\rho)$, which highly depends on μ_a. For given μ_s', γ and ρ values, the dependence of reflectance on μ_a is obtained by Monte Carlo results. From Equ.(7) we have:

$$\mu_a = h[\sqrt{R(\rho)} - f(\gamma, \mu_s')] \tag{13}$$

where f and h are functions given by Monte Carlo simulation. Particularly, they can be well approximated by polynomial functions. For example, for $\gamma=1.9$, probe refractive index of 1.5, sample refractive index of 1.4, optical fibers of diameter 200 μm, NA=0.37 (source and collection):

$$h = -0.002257 - 8.171y + 268.8y^2 \tag{14}$$

$$f = 0.01311 + 0.05184\mu_s' - 0.01974\mu_s'^2 + \tag{15}$$
$$0.003217\mu_s'^3 - 0.0001992\mu_s'^4$$

where $y = [\sqrt{R(\rho)} - f]$ $[mm^{-1}]$. μ_a is expressed in $[mm^{-1}]$.

Method 3

Equ.(7) also shows that relative measurements of μ_a, i.e. variation of μ_a from a known value μ_{ao}, is possible by measuring the variation of the parameter $\sqrt{R(\rho)}$:

$$\sqrt{R(\rho, \mu_s', \gamma, \mu_{ao})} - \sqrt{R(\rho, \mu_s', \gamma, \mu_a)} \tag{16}$$
$$= B(\mu_{ao}, \mu_s') - B(\mu_a, \mu_s')$$

This relation is illustrated in Fig.10 in the case of $\mu_{ao}=0$, $\rho=1$ mm, $\gamma=1.0$, 1.9 and 2.5, and

for $a'=1$ to 0.83. Fig.10 confirms that the influence of γ is weak in the quantity

$\sqrt{R(\rho, \mu_s', \gamma, \mu_a = 0)} - \sqrt{R(\rho, \mu_s', \gamma, \mu_a)}$. For known μ_s', the function $B(a')$ allows for the determi-

nation of a relative absorption change $\Delta\mu_a = \mu_a - \mu_{ao}$. Fig.10 illustrates the case $\mu_{ao} = 0$, but

any other value of μ_{ao} is possible. The interesting point is that $B(a')$ does not depend on

the phase function.

CLAIMS

1. A method for local and superficial (on the order of one transport mean free path) characterization of a turbid media using the following parameters:

   1) the refractive index n of the turbid media

   2) the absorption coefficient μ_a of the turbid media

   3) the reduced scattering coefficient μ_s' of the turbid media

   4) the phase function parameter $\gamma = (1-g_2)/(1-g_1)$ of the turbid media, where g_1 and g_2 are the first two moments of the phase function.

   and comprising the steps of:

   -measuring the spatially-resolved reflectance $R(\rho)$ or any quantity which allows for the indirect determination of the said spatially-resolved reflectance $R(\rho)$.

   -mathematically processing $R(\rho)$ to compute at least one of the said parameters (n, μ_a, μ_s', γ) or the relative variations of these said parameters.

2. The method of claim 1, wherein said spatially resolved reflectance is measured by an optical fiber probe as described by the first embodiment in section 3, and described on fig 5.a.

3. The method of claim 1 and 2. wherein said spatially resolved reflectance is measured by an optical fiber probe composed of n fibers. as described in the particular embodiment in section 3. and described on fig 5.b. giving the wavelength dependance of at least one of the parameters (n, μ_a, μ_s', γ)

4. The method of claim 1, wherein said spatially resolved reflectance is measured by a device put directly in contact to the turbid media, as described by the second embodiment in section 3 and described on fig 5.c..

5. The method of claim 1, wherein said spatially resolved reflectance is measured by non contact detection unit, as described by the third embodiment in section 3 and described on fig 5.d.

6. The method of claims 1 to 5, wherein the following processing is performed:

- fit of the measured reflectance R(ρ) to the function:

$$m_1\rho^{m_2}\exp(m_3\rho) \tag{17}$$

This fit gives the values for the parameters m_1, m_2 and m_3 . assuming that the expression $R = m_1\rho^{m_2}\exp(m_3\rho)$ gives a smooth function R(ρ).

The slopes $\frac{\partial}{\partial\rho}\sqrt{R(\rho)}$ and $\frac{\partial}{\partial\rho}(\ln R(\rho))$, or any mathematical combinations of these two latter quantities and R(ρ), can be obtained directly from analytical functions using the parameters m_1, m_2 m_3, or by numerical procedures from the function $R = m_1\rho^{m_2}\exp(m_3\rho)$.

7. The method of claims 1 to 6, wherein the absorption coefficient μ_a, the reduced scattering coefficient μ_s' and the phase function parameter γ are determined on the basis of a fit of the measured spatially-resolved reflectance R(γ, μ_s', μ_a, ρ) to a set of Monte Carlo simulations. or functions approximating Monte Carlo simulations.

8 . The method of claims 1 to 6, wherein the absorption coefficient μ_a, the reduced scattering coefficient μ_s' and the phase function parameter γ are determined on the basis of the following form of the reflectance:

$$R(\rho) = (A(\rho, \gamma, \mu_s') + B(\mu_a, \mu_s'))^2 \tag{18}$$

where the function $A(\rho, \gamma, \mu_s')$ and $B(\mu_a, \mu_s')$ depends also on the sources and detectors characteristics, and the refractive index of the sample.

9. The method of claims 1 to 6, wherein the reduced scattering coefficient μ_s' and the phase function parameter γ are determined on the basis of the quantity $\frac{\partial}{\partial \rho}\sqrt{R(\rho, \mu_s', \gamma)}$, which depends weakly on the absorption coefficient μ_a for $0.3 < \rho\mu_s' < 5$.

10. The method of claims 1 to 6, wherein the absorption coefficient μ_a is determined based on the equation:

$$\mu_a = h[\sqrt{R(\rho)} - f(\gamma, \mu_s')] \tag{19}$$

where f and h are functions that approximate Monte Carlo simulations.

11. The method of claims 1 to 6, wherein variation of the absorption coefficient μ_a from a known value μ_{ao} is computed from the variation of the parameters $\sqrt{R(\rho, \mu_s', \gamma, \mu_{ao})} - \sqrt{R(\rho, \mu_s', \gamma, \mu_a)}$.

12. The method of claims 1 to 10, wherein said turbid medium is a biological medium.

13. The method of claims 1 to 11, wherein the measurement an processing is repeated at different location of the sample (multi-site measurements), to build images of one of the said parameters (n, μ_a, μ_s', γ).

14. An apparatus for local and superficial characterization of a turbid media comprising a source, a detection unit, reference means, signal processing means, at least one source

connected to said source unit and at least one detector connected to said detection unit, the

distance between the source and the detector being less than one transport mean free path.

15. The apparatues of claim 14 charaterized by the fact that the distance between the

source and the detector varies from 0.1 to 2mm. for application to biological media and to

turbid media similar to biological media.

5

16. The apparatus of claim 14 or 15 using the method of any claim 1 to 13.

17. The apparatus of claim 16 where the control of the homogeneity of the probed sample

area is performed according to the procedure described in section 5.1.

18. The apparatus of claim 16 where the calibration and normalization procedures of sec-

tion 4. are carried out.

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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7   G01N21/49

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7   G01N   A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	F. BEVILACQUA ET AL: "In vivo local determination of tissue optical properties" SPIE, EUROPEAN BIOMEDICAL OPTICS, BIOS EUROPE 97, vol. 3194, 1997, pages 262-268, XP000866481 page 267, last paragraph page 265, line 7 -page 266, line 10 ---	1,12,14, 15
A	US 5 452 723 A (WU JUN ET AL) 26 September 1995 (1995-09-26) column 12, line 43 - line 54 column 10, line 21 - line 33 column 6, line 44 -column 7, line 15 --- -/--	1,14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2000	16/02/2000

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document. with indication,where appropriate. of the relevant passages	Relevant to claim No.
A	P. MARQUET ET AL: "DETERMINATION OF REDUCED SCATTERING AND ABSORPTION COEFFICIENTS BY A SINGLE CHARGE-COUPLED-DEVICE ARRAY MEASUREMENT, PART I: comparison between experiments and simulations" OPTICAL ENGINEERING, vol. 34, no. 7, July 1995 (1995-07), pages 2055-2063, XP002129315 abstract page 2057, left-hand column, line 1 -page 2058, left-hand column, line 6 ---	1,14
A	D.R. WYMAN ET AL: "Similarity relations for the interaction parameters in radiation transport" APPLIED OPTICS, vol. 28, no. 24, 15 December 1989 (1989-12-15), pages 5243-5429, XP000086704 page 5245, right-hand column, line 1 -page 5246, left-hand column, line 2 abstract -----	1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5452723 A	26-09-1995	NONE	